REMARKS

The present application is directed to a methods, kits and disposable units for performing a nucleic acid amplification reaction. Claims 1-6 and 8-35 were pending prior to the issuance of the June 1, 2005, Office Action. Following entry of this amendment, Claims 1-6 and 8-35 will be pending. Claims 34 and 35 are currently amended. No new matter is added, and support for the amendments may be found throughout the specification and in the original claims.

Claim rejections under 35 U.S.C. §103 (a)

In the Non-Final Office Action mailed June 1, 2005, the Examiner rejected Claims 1-5, 8, 14-16, 18, 25 and 26 under 35 U.S.C. §103(a), as being unpatentable over Beutler *et al.* (U.S. Patent No. 5,234,811) in view of Kris *et al.* (U.S. Patent 6,238,869) as evidenced by Heritz *et al.* (Journal of Urology). The Examiner states that Beutler *et al.* disclose a method of amplifying target nucleic acid, wherein the method involves the use of a buffer at pH 8.8, and the amplification reaction involving thermal cycling. Applicants respectfully traverse the rejection.

Applicant respectfully submit Beutler *et al.* fails to teach or suggest conducting an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth, as recited in pending Claim 1.

As discussed in the instant application, the claimed method utilizes a disposable unit having a thermally conducting layer and a high surface area:volume ratio, which allows rapid nucleic acid amplification (see page 2, lines 28-32 of the instant application). This aspect and advantage of the instant application is not taught or suggested by Beutler *et al.*

The deficiencies of Beutler *et al.* are not satisfied by the teachings of Kris *et al.* for at least the following reasons. Kris *et al.* disclose a high throughput assay system using 96-, 384-, and 1536-well microtiter plates. The microtiter plates are used as supports for high-throughput assays involving contacting a sample sequentially with various reagents to detect a nucleic acid target in the sample. It is important to note that the microtiter plates of Kris *et al.* fail

to teach or suggest the use of a thermally conducting layer and a facing layer as recited in pending Claim 1. Applicants respectfully submit that if the microtiter plate of Kris *et al.* contained both a thermally conducting layer and a facing layer, then reagents could not be added to the sample wells as required by the assay system of Kris *et al.*

Additionally, applicants respectfully submit that Kris *et al.* fail to teach or disclose microtiter plates with reagent wells of up to 1000 microns in depth as claimed herein. Furthermore, the microtiter plates of Kris *et al.* do not contain a thermally conducting layer and a facing layer having one or more regent wells of up to 1000 microns in depth defined therebetween as recited in Claim1.

Applicants respectfully submit there is no motivation to combine the teachings of Beutler *et al.* and Kris *et al.* Furthermore, the Examiner fails to provide any indication or logic as to why one of ordinary skill in the art would combine these two references. The PCR conditions of Beutler *et al.* disclose using a higher than exemplary buffer pH in the PCR reaction mixture, pH 8.8 (see example 1D, column 22, lines 25-36 of Beutler *et al*). Kris *et al.* disclose a high throughput assay involving sequential addition of various agents. Applicants respectfully submit that neither reference teaches, suggests or motivates one of ordinary skill in the art to arrive at the subject matter of pending Claim 1.

The deficiencies of Beutler *et al.* and Kris *et al.* are not satisfied by the teachings of Heritz *et al.* for at least the following reasons. Heritz *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

Claims 2-5, 8, 14-16, 18, 25 and 26 depend directly or indirectly from pending Claim 1. As discussed above, applicants respectfully submit that Claim 1 is non-obvious over the teachings of Beutler *et al.*, Kris *et al.*, and Heritz *et al.* For at least the foregoing, applicants respectfully submit that the subject matter of the invention is non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claims 1-5, 8, 14-16, 18, 25 and 26 under 35 U.S.C. §103(a).

The Examiner rejected Claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Kris *et al.* as evidence by Heritz *et al.* as applied to Claims 1-5, 8, 14-16, 18, 25 and 26 above, and further in view of Moss *et al.* (U.S. Patent No. 5,386,021). Applicants respectfully traverse.

Applicants reiterate their remarks in response to Beutler *et al.* and Kris *et al.* as evidence by Heritz *et al.* as applied to Claims 1-5, 8, 14-16, 18, 25 and 26 above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Kris *et al.* and Heritz *et al.* are not satisfied by Moss *et al.* for at least the following reasons. Moss *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1. Claim 6 depends directly from pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

For at least the foregoing, applicants respectfully submit that Claim 6 is non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claim 6 under 35 U.S.C. §103(a).

The Examiner has rejected Claims 19-20 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Kris *et al.*, as evidenced by Heritz *et al.* as applied to Claims 1-4, 8, 14-16, 18, 25 and 26 above and further in view of *Little et al.*, U.S. Patent No. 6,077,669. Applicants respectfully traverse.

Applicants reiterate their remarks in response to Beutler *et al.* and Kris *et al.* as evidence by Heritz *et al.* as applied to Claims 1-4, 8, 14-16, 18, 25 and 26 above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Kris *et al.* and Heritz *et al.* are not satisfied by Little *et al.* for at least the following reasons. Little *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1. Claims 19-20 depend directly or indirectly from pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

Additionally, applicants respectfully submit Little *et al.* teaches away from the use of reagents in dried form. Indeed, Little *et al.* recite that the use of dried reagents "has been found to cause an unreproducible fluorescence detection signal" (see column 2, lines 39-42). Applicants therefore respectfully submit one of ordinary skill in the art would not be motivated to modify the teachings of Little *et al.* to arrive at the subject matter of Claims 19 and 20.

For at least the foregoing, applicants respectfully submit that Claims 19-20 are non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claims 19-20 under 35 U.S.C. §103(a).

The Examiner has rejected Claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.*, in view of Kris *et al.*, as evidenced by Heritz *et al.* as applied to

Claims 1-4, 8, 14-16, 18 and 25 and further in view of Danssaert *et al.* Applicants respectfully traverse the rejection.

Applicants reiterate their remarks in response to Beutler *et al.* and Kris *et al.* as evidence by Heritz *et al.* as applied to Claims 1-4, 8, 14-16, 18, and 25 as above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Kris *et al.* and Heritz *et al.* are not satisfied by Danassert *et al.,* for at least the following reasons. Danassert *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1. Claims 22-24 depend directly or indirectly from pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

For at least the foregoing, applicants respectfully submit that Claims 22-24 are non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claims 22-24 under 35 U.S.C. §103(a).

The Examiner has also rejected Claims 1-5, 8-18, 21, 25-29, 32 and 33 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Ronchi (U.S. Patent No. 6,372,484) as evidenced by Heritz *et al.* Applicants respectfully traverse the rejection.

Applicant respectfully submit Beutler *et al.* fails to teach or suggest conducting an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth, as recited in pending Claim 1.

The deficiencies of Beutler *et al.* are not satisfied by the teachings of Ronchi *et al.* for at least the following reasons. Applicants submit that Ronchi *et al.* disclose an apparatus

for performing PCR and capillary electrophoresis in a single, integrated and disposable device. The apparatus comprises a PCR chamber, an electrophoresis channel, and a removable barrier between the chamber and the electrophoresis channel (see column 3, lines 56-59). The PCR chamber is defined by a cavity within a thin tab extended portion of the device (see column 3, lines 65-column 4, line 1), which cavity forms a PCR pouch defined by the walls of the cavity and two sealants such as polyester film with acrylic adhesives (see column 5, line 36-38 and lines 53-55). As an alternative, the PCR pouch can have a "thin bottom surface defined by the body", in which case a sealant is needed to form an upper surface of the PCR pouch (see column 5, lines 38-40). Ronchi *et al.* state that the integral bottom surface is deemed to be less preferable because its additional mass reduces heat transfer efficiency (see column 5, lines 40-44). The body of the apparatus disclosed by Ronchi *et al.* must be fabricated using a material that is compatible with the reagents and thermal conditions of both PCR and capillary electrophoresis (see column 6, lines 22-24). The apparatus of Ronchi *et al.* is used to conduct PCR reactions in a standard PCR cycler (see example 1, column 8-9) prior to performing capillary electrophoresis on the PCR product.

The Examiner concluded that one of ordinary skill in the art would be motivated to employ the reaction involving the reaction conditions of Beutler *et al.* in the closed, sealed environment disclosed by Ronchi *et al.* for the advantage of conducting PCR in a sealed environment with a reasonable expectation of success. Applicants respectfully traverse.

The PCR reactions of Beutler *et al.* use a DNA Thermal Cycler (see column 20, lines 1-4). Applicants respectfully submit that a DNA Thermal Cycler typically requires the use of a tube (microcentrifuge). Support for this statement can be found in Beutler *et al.,* (column 11, lines 15-16) wherein U.S. 4,965,199 (hereinafter '199) is referenced for further details on PCR amplification methods. Patent '199 describes a preferred PCR machine of the type used by Beutler *et al.,* which has a "heat-conducting container for holding a given number of tubes, preferably 500µl tubes" (see U.S. 4,965,199; column 14, lines 9-10). Applicants respectfully submit that one of ordinary skill in the art would not be motivated to combine the teachings of Beutler *et al.* and Ronchi et *al.* for the advantage of conducting PCR in a sealed environment

with a reasonable expectation of success because Beutler *et al.* alone discloses a PCR reaction in a closed environment (a tube) without arriving at the claimed subject matter.

Furthermore, as discussed in the instant application, a disposable unit having a thermally conducting layer and a high surface area:volume ratio allow rapid nucleic acid amplification (see page 2, lines 28-32 of the instant application). This aspect and advantage of the instant application is not taught or suggested by Beutler *et al.* Applicants respectfully submit neither Beutler *et al.* or Ronchi *et al.* teach or suggest employing the reaction mixture of Beutler *et al.* in an apparatus disclosed by Ronchi *et al.* Additionally, applicants further submit that there is no motivation for one of ordinary skill in the art to use the reaction mixture of Beutler *et al.*, which comprises BSA or a higher than exemplary buffer pH (pH 8.8) in a PCR reaction mixture (see example 1D). Applicants respectfully submit neither reference teaches or suggests one of ordinary skill in the art to arrive at the subject matter as claimed herein. The mere fact that Ronchi *et al.* and Beutler *et al.* can be combined does not render the claimed invention obvious for at least the foregoing reasons.

The deficiencies of both Beutler et *al.* and Ronchi *et al.* are not satisfied by Heritz *et al.* Heritz *et al.*, fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

Similarly, no motivation or suggestion exists for one of ordinary skill in the art to combine Beutler *et al.* and Ronchi *et al.* regarding the "conventionality of kits in the analytical arts" to arrive at the subject matter of Claims 27 and 28 as suggested by the Examiner on pages

9-10 of the Office Action. For at least the foregoing, applicants respectfully submit the pending claims are non-obvious over the prior art.

With regard to independent Claim 29, the apparatus of Ronchi *et al.* contains a single PCR chamber, an electrophoresis channel and a removable barrier between the chamber and the channel. The removable barrier is adjusted to allow PCR product from the single PCR chamber to enter a sample well in the electrophoresis channel for capillary electrophoresis. (see column 4, lines 22-32). One of ordinary skill in the art would understand that only one PCR chamber is require in the apparatus of Ronchi *et al.* because the apparatus is "for performing both polymerase chain reaction and capillary electrophoresis for a single sample in a single disposable device" (emphasis added) see column 3, lines 52-55.

Furthermore, applicants respectfully submit the apparatus of Ronchi *et al.* has a sample charge port by which the sample enters the device and "a vent channel for venting a first sample well to ambient atmosphere" (see column 4, lines 3-6). In contrast, the instant invention discloses a disposable unit having multiple reagent wells which are fed by a common channel including a single opening to ambient atmosphere (see page 8, lines 8-11 of the instant application). Ronchi *et al.* fail to suggest or motivate one of ordinary skill in the art to modify the apparatus of Ronchi *et al.* to arrive at the disposable unit of Claim 29.

Applicants respectfully submit that independent Claims 1, 27 and 29 are non-obvious over the prior art of record for at least the foregoing reasons. In addition, Claims 2-5, 8-18, 21, 25-26, 28, 32 and 33 depend directly or indirectly from pending Claim 1. As discussed above, applicants respectfully submit that the pending claims are non-obvious over the teachings of Beutler *et al.*, Ronchi *et al.*, and Heritz *et al.* Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claims 1-5, 8-18, 21, 25-29, 32 and 33 under 35 U.S.C. §103(a).

The Examiner also rejected Claim 6 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Ronchi, as evidenced by Heritz *et al.* as applied to

Claims 1-5, 8-18, 21, 25-29, 32 and 33 above and further in view of Moss *et al.* Applicants respectfully traverse.

Applicants reiterate their remarks in response to Beutler *et al.* and Ronchi *et al.* as evidence by Heritz *et al.* as applied to Claims 1-5, 8-18, 21, 25-29, 32 and 33 above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Ronchi *et al.* and Heritz *et al.* are not satisfied by Moss *et al.* for at least the following reasons. Moss *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1. Claim 6 depends directly from pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

For at least the foregoing, applicants respectfully submit that Claim 6 is non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection of Claim 6 under 35 U.S.C. §103(a).

The Examiner rejected Claims 19, 20, 30 and 31 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Ronchi, as evidenced by Heritz *et al.* as applied to Claims 1-4, 8-18, 21, 25-29, 32 and 33 above, and further in view of Little *et al.* Applicants respectfully traverse.

Applicants reiterate their remarks in response to Beutler *et al.* and Ronchi *et al.* as evidence by Heritz *et al.* as applied to Claims 1-4, 8-18, 21, 25-29, 32 and 33 above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Ronchi *et al.* and Heritz *et al.* are not satisfied by Little *et al.*, for at least the following reasons. Little *et al.* fail to suggest or disclose a method of carrying out an amplification reaction in a disposable unit,

wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

Additionally, applicants respectfully submit Little *et al.* teaches away from the use of reagents in dried form. Indeed, Little *et al.* recite the use of dried reagents "has been found to cause an unreproducible fluorescence detection signal" (see column 2, lines 39-42). Applicants therefore respectfully submit one of ordinary skill in the art would not be motivated to modify the teachings of Little *et al.* to arrive at the subject matter of Claims 19, 20, 30 and 31.

For at least the foregoing, applicants respectfully submit that Claims 19, 20, 30 and 31 are non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. §103(a).

The Examiner has rejected Claims 22-24 under 35 U.S.C. § 103(a) as being unpatentable over Beutler *et al.* in view of Ronchi, as evidenced by Heritz *et al.* as applied to Claims 1-4, 8-18, 21, 25-29, 32 and 33 above, and further in view of Danssaert *et al.* Applicants respectfully traverse.

Applicants reiterate their remarks in response to Beutler *et al.* and Ronchi *et al.* as evidence by Heritz *et al.* as applied to Claims 1-4, 8-18, 21, 25-29, 32 and 33 above. Additionally, applicants respectfully submit that the deficiencies of Beutler *et al.*, Ronchi *et al.* and Heritz *et al.* are not satisfied by Danassert *et al.*, for at least the following reasons. Danassert *et al.* fails to suggest or disclose a method of carrying out an amplification reaction in a disposable unit, wherein the disposable unit comprises a thermally conducting layer and a facing layer having one or more reagent wells of up to 1000 microns in depth as recited in pending Claim 1.

Applicants respectfully submit there is no teaching or suggestion to motivate one of ordinary skill in the art to apply one or more of the reaction mixture ingredients specified in Claim 1 with the specific type of disposable unit recited in Claim 1 in order to overcome problems associated with conducting an amplification reaction in the claimed disposable unit (see page 2, lines 20-26 of the instant application).

For at least the foregoing, applicants respectfully submit that Claims 22-24 are non-obvious over the prior art. Accordingly, applicants respectfully request withdrawal of the Examiner's rejection under 35 U.S.C. §103(a).

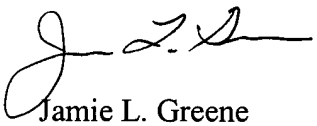
CONCLUSION

The foregoing is submitted as a complete Response to the Non-Final Office Action mailed on June 1, 2005. For at least the reasons given above, applicants submit that the claims in the present application are in condition for allowance, and such action is courteously solicited.

No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

If the Examiner believes that any informalities remain in the case, which may be corrected by Examiner's amendment, or that there are any other issues which can be resolved by a telephone interview, a telephone call to the undersigned attorney at (404) 815-6500 is respectfully solicited.

Respectfully submitted,



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